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Full length article

Prenatal counseling of an isolated fetal small head circumference during the second trimester expert ultrasound examination

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ABSTRACT

Objective: To evaluate perinatal and postnatal outcomes of fetuses with an isolated small head circumference (HC) on expert ultrasound examination in the second trimester for further recommendations in prenatal care.
Study Design: In a retrospective cohort we included singleton-pregnancies with a fetal HC > −3.0 SD and ≤ −1.64 SD determined on expert ultrasound examination between 18 and 24 weeks of gestational age. Three subgroups were determined: "isolated small HC (ISHC)", "small HC plus abdominal circumference (AC) ≤ p10 (SHC+)" and "small HC plus AC ≤ p10 and Doppler abnormalities (SHC + D)". After ultrasound examination, genetic testing was sometimes offered and postnatally genetic tests were performed on indication.
Results: We included 252 pregnancies: 109 ISHC, 104 SHC+, and 39 SHC + D. In the ISHC and SHC+ subgroup, 96 % of the fetuses were born alive and did not die neonatal. In the SH + D group this was only 38 %. In the SHC+ subgroup, less fetuses were delivered vaginal (non-instrumental) compared to the ISHC subgroup (61 % vs. 73 %, p < 0.01). In the ISHC and SHC+ subgroup s some fetuses were diagnosed with congenital defects (4 % vs. 10 %, p = 0.08) and with a genetic anomaly (6.4 % vs. 7.7 %, p = 0.13) after 24 weeks or postnatally. In SHC + D subgroups 5 % presented with congenital defects and 2.6 % with a genetic anomaly.
Conclusion: We conclude that fetuses with a small HC without structural anomalies on second trimester expert ultrasound require follow-up and special medical attention. We recommend differentiating between ISHC, SHC+, and SHC + D for prenatal counseling. Genetic testing and referral to a clinical geneticist should be considered.

Introduction

A small fetal head circumference (HC) (≤2.3th percentile [1]) is a common reason for referral to a fetal medicine center after second trimester standard structural ultrasound examination in the Netherlands. Differentiation between a physiological small head, a smaller head due to an underlying problem, or microcephaly is important to predict prognosis and to determine counseling management. To classify the HC, the WHO currently recommends the Intergrowth-21st criteria if the gestational age (GA) is known [2].

Additional examination of the developing brain would be helpful, however, diagnosing malformations of cortical development before the 24th week of GA is challenging [3]. Serial ultrasound measurements of fetal biometry could provide more information. However, in the Netherlands, termination of pregnancy (ToP) may only be carried out until the 24th week of pregnancy. After 24 weeks of pregnancy ToP is strictly limited to cases in which severe and lifelong health problems, and unbearable suffering are to be expected for the fetus, and decision on this procedure should be reported to the assessment committee for late ToP. Thus, the available time period for additional testing and informed decision making is limited. Genetic testing can be offered, but its value when the HC is ≤2.3th percentile but >−3 SD has not been established. Measurements of the parental HC can be reassuring; however, a small parental HC as argument for a physiologic small fetal head has not been proven.

Microcephaly is a developmental disorder of the central nervous system. The main clinical prenatal ultrasound feature is a decreased HC [4,5]. Microcephaly is generally defined as a HC ≤ −3 standard deviation (SD), because of the correlation with intellectual disability [5,6]. In case of a HC ≤ −3 SD, the prenatal management is standardized;

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Table 1
General characteristics of the total study population and the subgroups ISHC, SHC+ and SHC + D.

	Total (n = 252)	ISHC (n = 109)	SHC+ (n = 104)	P-value	SHC + D (n = 39)	missing
Maternal characteristics						
Age, years, mean ± SD	30.4 (5.6)	30.6 (5.3)	30.5 (5.9)	0.98	29.3 (5.6)	0
Primigravid, n (%)	80 (32)	26 (24)	31 (30)	0.35	23 (59)	0
Nulliparous, n (%)	108 (43)	40 (37)	37 (36)	0.87	31 (80)	0
GA at diagnosis (days), median (range)	150 (137–168)	148 (138–166)	151 (137–168)	0.06	147 (138–165)	0
Geographic origin, n (%)				0.33		
Dutch	130 (52)	65 (61)	47 (45)		18 (46)	2
Other Western	32 (13)	11 (10)	16 (15)		5 (13)	
Non-Western	77 (31)	28 (26)	35 (34)		14 (36)	
Mixed Western and Non-Western	11 (4)	4 (4)	5 (5)		2 (5)	
Fetal characteristics						
Fetal sex, n (%)				0.09		0
Male	59 (23)	17 (16)	26 (25)		16 (41)	
Female	193 (77)	92 (84)	78 (75)		23 (59)	
Fetal HC percentile, median (range)	1.0 (0–2.3)	1.2 (0–2.3)	0.8 (0–2.2)	**<0.01**	0.3 (0–2.0)	0
Fetal HC SD, median (range)	−1.9 (-2.97- −1.64)	−1.89 (-2.69- −1.64)	−2.02 (-2.97- −1.64)	**<0.01**	−2.27 (-2.87- −1.69)	0
Non-structural anomalies, n (%)‡	40 (15)	14 (13)	13 (13)	0.62	11 (28)	0

Data is presented as mean and standard deviation (SD), median and range or number (n) and percentage (%). Significant findings are marked in bold and red.
ISHC, isolated small head circumference; SHC+, small head circumference plus; SHC + D, small head circumference plus and Doppler anomalies; GA, gestational age; HC, head circumference; mm, millimeter; n, number; SD, standard Deviation; %, percentage.
† i.e. *in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI).*
‡ i.e. *single umbilical artery, echogenic bowel, pyelectasis, echogenic cardiac focus, choroid plexus cyst(s) and/or sandal gap.*

additional genetic counseling/testing, serial detailed neurosonography, screening for infections, and follow-up by ultrasound are offered [7]. However, when the HC is small, but >−3 SD, the prenatal management strategy is uncertain.

Therefore, in this retrospective study, we aim to investigate perinatal and postnatal outcomes of fetuses with a small HC without structural anomalies (or suspicion of microcephaly) on expert ultrasound at 18–24 weeks GA, to provide recommendations to improve the management of prenatal counseling and medical care.

Materials and methods

Study design and population

This is a retrospective cohort study of patients attending the division of Obstetrics and Fetal Medicine of the Department of Obstetrics and Gynecology at the Erasmus Medical Center, Rotterdam, the Netherlands, from January 2012 until January 2019. We included all singleton pregnancies with a fetal HC > −3.0 SD and ≤−1.64 SD (equal to ≤2.3th percentile according to the Verburg growth charts [1]) determined on expert ultrasound examination between 18 (126 days) and 24 (168 days) weeks GA. The ultrasounds were performed by trained fetal medicine specialists or doctors specialized in fetal diagnosis. Standard deviations were determined based on the Intergrowth-21st criteria [2]. Fetuses with structural anomalies, including brain abnormalities, discovered on ultrasound, were excluded from this study. Pregnancies with preterm pre-labor rupture of membranes (PPROM), with a proven CMV infection, and/or a maternal condition that poses an independent risk for poor outcome (such as antiphospholipid syndrome) were excluded from the study due to the additional (severe) impact on obstetric and fetal outcome. Pregnancies that were lost to follow-up were excluded. In case of a non-structural anomaly (i.e. single umbilical artery, echogenic bowel, pyelectasis, echogenic cardiac focus, choroid plexus cyst(s), and/or sandal gap) patients were included for analysis.

Study parameters

At the first appointment in the Erasmus MC after referral for expert ultrasound examination patients gave written consent for collecting follow-up data after delivery. Data on maternal characteristics, pregnancy course and diagnostic genetic testing were obtained from the ultrasound and medical patient file. Data on pregnancy outcomes were obtained from the delivery reports of the Erasmus MC or sent to our center upon request. Approval of the study was obtained from the regional Medical Ethical and Institutional Review Board.

Ultrasound measurements and additional testing

The ultrasound examinations were performed using high-quality ultrasound equipment (Voluson E8 or E10 system, GE Medical Systems, Zipf, Austria, RM6C abdominal probe). During ultrasound examinations, biometry measurements and a total structural examination of the fetus were performed. When indicated (in case of an abdominal circumference (AC) ≤ 10th percentile), Doppler measurements of the umbilical artery and middle cerebral artery were performed.

After ultrasound examination, some patients were offered genetic testing; i.e. amniocentesis followed by 0.15 Mb array analysis [8,9]. However, in this time period, there was no uniform policy in offering prenatal (genetic) counseling. Postnatally, genetic tests were performed on indication, including 0.15 Mb array analysis and/or whole exome sequencing (WES).

TORCH/parvo B19 analysis was not offered routinely, only offered in a few cases on clinical indication.

The study population was divided into three subgroups: “isolated small HC (ISHC)”, “small HC plus (SHC +)” and “small HC plus Doppler abnormalities (SHC + D)”. ISHC was defined as an abdominal circumference (AC) > 10th percentile along the small HC. SHC + was defined as a small HC combined with an AC ≤ 10th percentile. SHC + D was defined as SHC + and Doppler abnormalities (absent or reversed end diastolic flow (EDF) in the umbilical artery and/or a cerebroplacental ratio (CPR) below 1.00). Small for gestational age (SGA) was defined as a birthweight ≤ 10th percentile. The Fenton growth chart was used to determine birth weight percentiles, HC percentiles and SD [10,11]. Additional analysis comparing male to female fetuses was performed. The SHC + D subgroup was described separately because it was expected to be of different etiology and the current counseling of this group according to protocol is drastically different from the ISHC and SHC+ subgroup. The latter were compared directly.

Table 2
Obstetric and neonatal outcomes of the total study population and subgroups ISHC, SHC + and SHC + D.

	Total (n = 252)	ISHC (n = 109)	SHC+ (n = 104)	P-value	SHC + D (n = 39)	missing	General population Netherlands [1]
Pregnancy Outcome							
Live birth†, n (%)	220 (87)	105 (96)	100 (96)	0.95	15 (38)	0	
IUFD, n (%)	14 (6)	1 (1)	1 (1)	0.97	12 (31)		
Termination of Pregnancy, n (%)	9 (4)	1 (1)	3 (3)	0.29	5 (13)		
Neonatal Death, n (%)	9 (4)	2 (2)	0 (0)	0.17	7 (18)		
Mode of delivery							
Vaginal non-instrumental, n (%)	162 (64)	80 (73)	63 (61)	**<0.05**	19 (49)	0	**74 %**
Caesarean, n (%)	71 (28)	17 (16)	35 (33)	**<0.01**	19 (49)		**17 %**
Elective caesarean	49 (19)	9 (8)	23 (22)	**<0.01**	17 (44)		
Secondary caesarean	14 (6)	6 (6)	7 (7)	0.71	1 (3)		
Emergency caesarean	8 (3)	2 (1)	5 (5)	0.22	1 (3)		
Vaginal instrumental, n (%)	19 (8)	12 (11)	6 (6)	0.17	1 (3)		**8 %**
GA at birth (days), median (range)	255 (159–293)	272 (165–293)	267 (159–292)	**0.03**	192 (160–293)	0	
Postnatal							
Birthweight percentile, median (range)	13 (0–96)	26 (0–96)	9 (0–76)	**<0.01**	1 (0–20)	0	
Birthweight ≤ p10, n (%)	113 (45)	22 (20)	53 (51)	**<0.01**	38 (97)	1	
HC percentile, median (range)	7 (0–100)	14 (0–100)	7 (0–95)	**0.03**	0.5 (0–91)	0	
HC ≤ p2,3, n (%)	41 (35)	7 (15)	12 (28)	0.12	22 (79)	133	
HC ≤ p10, n (%)	69 (58)	20 (42)	24 (56)	0.18	25 (89)	133	
Congenital defects, n (%)						14	
Yes	20 (8)	4 (4)	10 (10)	0.08	6 (15)		
None	218 (87)	102 (94)	89 (86)	0.06	27 (69)		
One	12 (5)	1 (1)	5 (5)	0.09	6 (15)		
Multiple	8 (3)	3 (3)	5 (5)	0.43	0 (0)		
Unknown	14 (6)	3 (3)	5 (5)	0.43	6 (15)		
Genetic testing, n (%)						209	
Cytogenomic aberration‡	16 (4.7)	7 (6.4)	8 (7.7)	0.13	1 (2.6)		
Unknown (not tested/no follow-up available)	209 (83)	100 (92)	87 (84)		22 (56)		

Data is presented as median and range or number (n) and percentage (%) of all-in subgroup. Significant findings are marked in bold and red.
ISHC, isolated small head circumference; SHC+, small head circumference plus; SHC + D, small head circumference plus and Doppler anomalies; IUFD, intrauterine fetal death; HC, head circumference; n, number; %, percentage.
†*without neonatal death,* ‡*causal for small HC.*
[1]Euro-Peristat. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015 - Mode of Delivery *Available wwweuroperistatcom* 2018.

Statistical analysis

Data analysis was performed using SPSS (SPSS release 21 for Windows, IBM, United States of America). Probability values ≤ 0.05 were considered statistically significant. Descriptive statistics calculated the general characteristics and outcomes for the total study population. General characteristics and outcomes of the subgroups were compared using independent sample t-tests for normally distributed continuous data, Mann-Whitney *U* test for non-normally distributed continuous data, and Chi-square tests for categorical data.

Results

A fetal HC > −3.0 SD and < −1.64 SD (equal to ≤ 2.3th percentile [1]) without structural anomalies (with follow-up), was detected in 252 patients. 109 fetuses had an ISHC, 104 fetuses had a SHC+ and 39 fetuses had a SHC + D. The characteristics of the included pregnancies are depicted in Table 1. 77 % of the included fetuses were phenotypically female. The fetuses in the SHC+ subgroup had a significantly smaller fetal HC than the ISHC fetuses (-2.02 SD vs. −1.89 SD; p < 0.01). There were no other statistically significant differences in characteristics.

The obstetric and neonatal outcomes are shown in Table 2. Fig. 1 shows the flowchart of the obstetric outcome per subgroup. In the ISHC and SHC+ subgroup, 96 % of the fetuses were born alive (without neonatal death). In the ISHC subgroup one fetus (1 %) died intra uterine (IUFD) (due to abruption of the placenta). There was one ToP (1 %), after the diagnosis of Turner syndrome. There were two neonatal deaths (2 %) due to necrotizing enterocolitis. In the SHC+ subgroup, there was one IUFD (1 %) and there were three ToP (3 %). The IUFD occurred due to severe fetal growth restriction (FGR) with birthweight at 1th percentile. Two ToP took place because of severe FGR with poor prognosis and one because of the genetic diagnosis of trisomy 21. In the SHC+ subgroup, fewer fetuses were delivered vaginal (non-instrumental) compared to the ISHC subgroup (61 % vs. 73 %, p < 0.01). More caesarian sections were performed in the SHC+ subgroup than in the ISHC subgroup (34 % vs. 16 %, p < 0.01). In the SHC+ subgroup, significantly more fetuses were SGA (51 % vs. 20 %, p < 0.01).

Four infants (4 %) in the ISHC subgroup were diagnosed postnatally with one or multiple congenital defects. In two of these infants (50 %) there was a genetic diagnosis that is likely to be causally connected, and in one a susceptibility copy number variant (sCNV) that seems to be explanatory to the small HC was found [12,13]. Seven fetuses of the ISHC subgroup (6.4 %) were diagnosed with genetic diagnoses which can cause a small HC before or after birth (12 % and 5.4 % of male and female fetuses respectively). The following genetic diagnoses were identified: trisomy 21 (4), trisomy 21 in combination with Klinefelter syndrome (1), Turner syndrome (1) and 15q13.2q13.3 microdeletion (1) (sCNV that seem to be explanatory to the small HC [12,13]) (Table 3).

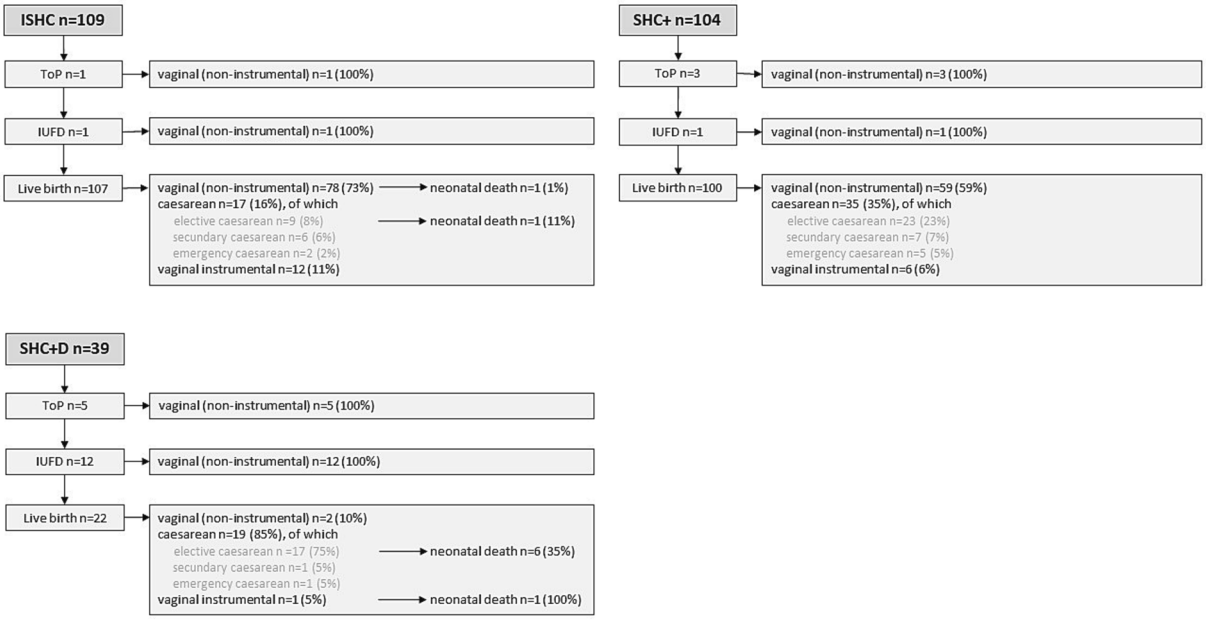

Fig. 1. Flowchart of the obstetric outcome per subgroup (ISHC, SHC + and SHC + D) *ISHC, isolated small head circumference; SHC+, small head circumference plus; SHC + D, small head circumference plus and Doppler anomalies; n, number; %, percentage; ToP, termination of pregnancy; IUFD, intrauterine fetal death.*

Additionally, one incidental monogenetic anomaly (Gilbert syndrome) was found in the ISHC subgroup.

Ten infants (10 %) in the SHC+ subgroup were diagnosed with one or multiple congenital defects. In three of the ten infants with congenital anomalies, a genetic anomaly was found (30 %), and in one a sCNV that seems to be explanatory to the small HC [14,15]. In the SHC+ subgroup, eight fetuses (7.7 %) were diagnosed with a genetic anomaly before or after birth (8 % and 7.7 % of male and female fetuses respectively). The anomalies were trisomy 21, MECP2 duplication syndrome, Silver-Russell syndrome, Smith-Lemli-Opitz syndrome, and Fanconi anemia (Table 3). Additionally, three sCNV's (22q11.21 microduplication, 16p13.11 microduplication, and 16p12.2 microdeletion) matching the phenotype were found in the SHC+ subgroup (Table 3) [14–17].

In the SHC + D subgroup, fifteen pregnancies resulted in a live birth (38 %) (without neonatal death), twelve in an IUFD (31 %), five in a ToP (13 %), and seven in neonatal death (18 %). The IUFDs occurred due to severe FGR with birth weight ≤ 3th percentile. ToP was requested in four cases due to severe FGR and once due to severe pre-eclampsia**.** Six neonatal deaths occurred due to bronchopulmonary dysplasia after extreme or very preterm birth and one due to sepsis due to necrotizing enterocolitis combined with a severe immunodeficiency. 49 % of the SHC + D fetuses were delivered vaginal (non-instrumental), 49 % via caesarean, and one vaginal instrumental (3 %). At birth 97 % of these fetuses were SGA, 79 % had a HC ≤ 2.3th percentile and 89 % had a HC ≤ 10th percentile. Six fetuses (15 %) were diagnosed with a congenital defect post-partum. One fetus (2.6 %) was diagnosed with a sCNV matching the phenotype after birth: 15q11.2 microdeletion (Table 3) [18]. Additionally, one incidental genetic diagnosis (adenosine deaminase severe combined immunodeficiency (ADA-SCID)) was found in the SHC + D subgroup.

Discussion

In our study we investigated the outcome of fetuses diagnosed with a small head, without suspicion of structural anomalies on expert fetal ultrasound in mid-pregnancy in a tertiary referral hospital setting. We aimed to provide recommendations to improve prenatal counseling. Our results indicate that this group of patients requires special obstetrical care, as well as prenatal and postnatal investigation and follow-up. FGR, genetic anomalies and congenital malformations occur in a higher percentage in this group than in the general population.

In the SHC + D subgroup, Doppler anomalies are strong indicators for placental failure giving these fetuses a poorer prognosis [19]. These fetuses have a small HC without other congenital malformations, fitting our inclusion criteria. However the small HC is only part of (severe) abnormal fetal growth. It is obvious that these pregnancies need special medical attention. Recommendations for this subgroup are as presented in literature: fetal follow-up by ultrasound as per local protocol and offering genetic diagnostic testing [20,21]. Multidisciplinary counseling by neonatology and a fetal medicine specialist in this subgroup is very important.

We focused on the ISHC and SHC+ groups, because the results of these groups are most relevant to our research question. A relatively high percentage of genetic diagnoses were found in the ISHC and SHC+ subgroup. Most were diagnosed after birth as genetic testing was not routinely offered during the pregnancy or because of rejection of the future parents. In the ISHC subgroup the number of fetuses with trisomy 21 cannot be explained by maternal age. In the SHC+ group, we detected genetic anomalies with clinical impact after birth by microarray and/or WES. The sCNVs found in our study population seem to be explanatory but might not be the only factor causing the abnormal phenotype. The second hit theory hypothesizes that two genomic events act independently and that the simple addition of their effects can lead to developmental differences [22]. However, we do assert an underestimate of genetic diagnoses in our study population because genetic testing was not conducted in most of these pregnancies and because exome sequencing was not available for prenatal diagnostics in that time period. The detection of genetic variants as a syndromic cause of fetal anomalies may be especially valuable in cases with a less severe phenotype or with an apparent isolated anomaly. Many syndromes have postnatal features that cannot be detected prenatally e.g., intellectual disability or hypotonia [23]. A molecular diagnosis puts the ultrasound finding(s) in a different perspective to future parents. It might have an impact on decision-making during pregnancy or neonatal management. Therefore, the opportunity for genetic diagnostic testing (microarray) should be included in the prenatal counseling of fetuses with a small HC. Referral to a clinical geneticist for WES counseling could be considered given the genetic diagnoses found by WES in our study without it being

Table 3
Genetic diagnoses in the total study population.

#	Genetic diagnosis	Subgroup	Period of diagnosis	Cytogenetic results	Causality for small HC	OMIM/ICD code	Comment
1	Down syndrome	ISHC	postnatal	Trisomy 21	causal	OMIM #190685 ICD-10: Q90.2	denied FTS
2	Down syndrome	ISHC	postnatal	Trisomy 21	causal	OMIM #190685 ICD-10: Q90.2	denied FTS
3	Down syndrome	ISHC	postnatal	Trisomy 21	causal	OMIM #190685 ICD-10: Q90.2	first-trimester combined screening: no increased risks, denied amniocentesis
4	Down syndrome	ISHC	postnatal	Trisomy 21	causal	OMIM #190685 ICD-10: Q90.2	too late for FTS
5	Down syndrome and Klinefelter syndrome	ISHC	postnatal	Trisomy 21 and XXY	causal	OMIM #190685/#40045 ICD-10: Q90.2/Q98.4	denied FTS
6	Turner syndrome	ISHC	prenatal < 24w GA	Monosomy X	causal	OMIM: - ICD-10: Q96.0 Q96.1 Q96.2 Q96.3 Q96.4 Q96.8 Q96.9 ICD-11: LD50.0	
7	15q13.2q13.3 microdeletion	ISHC	postnatal	arr[hg19] 15q13.2q13.3 (30940504_32515100)x1	phenotype matching sCNV[2, 3]	OMIM #612001 ICD-10: Q93.5	1.6 Mb 15q13 microdeletion – sCNV for variable phenotype, and associated with mild to moderate mental retardation and epilepsy [2, 3]. Age of 18 months: West syndrome (clinical diagnosis) OMIM #300672, 308350, 613477, 613722, 615006, 616139, 616341, 617065, 617929, 618,298 ICD-10: G40.4 ICD-11: 8A62.0
8	Gilbert syndrome	ISHC	postnatal	Monogenetic anomaly: Heterozygosity for c.211G > A, p.(Gly71Arg) mutation	no, incidental finding	OMIM #143500 ICD-10: E80.4	DNA-diagnostics for UGT1A1-gene, CMA not performed
9	MECP2-duplication syndrome	SHC+	postnatal	arr[hg19] Xp22.33 (60814_1504278)x1 mat, Xq28 (152559458_155236712)x3 mat (male fetus)	causal	OMIM #300260 ICD-10: Q92. 5	Loss of ca. 1,4 Mb in band Xp22.33 and gain of ca. 2,7 Mb in band Xq28 (recombinant X-chromosome) causing SHOX deletion and MECP2-duplication syndrome
10	Silver-Russell syndrome	SHC+	postnatal	Hypomethylation of the H19 gene, normal CMA	causal	OMIM #180860, 312780, 616489 ICD-10: Q87.1	NIPS normal
11	Down syndrome	SHC+	prenatal < 24w GA	Trisomy 21	causal	OMIM #190685 ICD-10: Q90.2	FTS not offered, maternal age 37 years
12	Smith Lemli Opitz syndrome	SHC+	postnatal	Normal CMA, c.808A > G(p.Met270Val) en c.964-1G > C (splicing defect) in DHCR7 gene	causal	OMIM #270400 ICD 10: Q87.1	
13	22q11.21 microduplication	SHC+	postnatal	arr[hg18] 22q11.21 (17280064_19338540)x3 mat	phenotype matching sCNV[4]	OMIM #608363 ICD-10: Q92.3	2 Mb 22q11 microduplication (sCNV) denied FTS and amniocentesis
14	Fanconi anemia	SHC+	postnatal	Normal CMA	causal	OMIM #227645, 227646, 227650, 300514, 600901, 603467, 609053, 609054, 610832, 613390, 613951, 614082, 614083, 615272, 616435, 617243, 617244, 617247, 617883 ICD 10: D61.0	Mitomycin C test positive for Fanconi anemia
15	16p13.11 microduplication	SHC+	prenatal < 24w GA	arr[hg19] 16p13.11 (14,968,859–16,311,466)x3 mat	phenotype matching sCNV[5, 6]	OMIM: - ICD-10: Q92.3	NDE1 gene[7]
16	16p12.2 microdeletion	SHC+	prenatal < 24w GA	arr[hg19] 16p12.2 (21839340_22409463)x1 pat	phenotype matching sCNV[8]	OMIM #613604 ICD-10: Q93.5	16p12.2 microdeletion (paternally inherited) sCNV
17	15q11.2 microdeletion	SHC + D	postnatal	arr[hg 18] 15q11.2 (20,070,582–21,025,923)x1	phenotype matching sCNV[9]	OMIM #615656 ICD-10: Q93.5	denied amniocentesis
18	ADA-SCID	SHC + D	postnatal	Normal CMA	no, incidental finding	OMIM #102700 ICD-10: D81.3	pathogenic variant in ADA gene (20q13.12)

#, number; ISHC, isolated small head circumference; SHC+, small head circumference plus; SHC + D, small head circumference plus and Doppler anomalies; GA, gestational age; w, weeks; FTS, first trimester screening; HC, head circumference; NIPS, non-invasive prenatal screening; sCNV, susceptibility copy number variant; ICD, International

Classification of Diseases; OMIM, Online Mendelian Inheritance in Man; ADA-SCID, adenosine deaminase severe combined immunodeficiency; CMA, Chromosomal microarray.
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offered to all cases. Further studies on the value of WES in this population need to be performed.

Pregnancy outcome is similar between the ISHC and SHC+ subgroups. The viability of fetuses in these subgroups is relatively good. Rates of mode of delivery in the ISHC subgroup are comparable with the general rates in the Netherlands [24,25]. This implies that an ISHC is not an obstetric risk factor for mode of delivery and does not require more monitoring or supervision at birth than the general population. After additional prenatal genetic testing with normal results patients could be referred back to normal obstetric care. Additionally, to determine the best place for delivery, monitoring of prenatal growth is important.

The high percentage of female fetuses in our study population is remarkable. It is known that male fetuses have a higher growth rate compared to females in singleton pregnancies [26,27]. However, our results are not showing a difference in genetic diagnoses between fetal sexes, possibly due to lack of statistical power because of the small number of patients in both subgroups.

Internationally, different prenatal growth charts are used, which could have biased the results. In the Netherlands, the most commonly used for determination of percentiles is the Verburg growth chart (based on the Dutch population) [1]. The internationally licensed Intergrowth-21st criteria standardized growth chart is a common source for determination of the SD and was therefore chosen in this study [2]. The most common congenital defect detected postnatally in our study population is microcephaly. Unfortunately, pre- and postnatal growth charts are different and do not overlap exactly. Furthermore, the definition of microcephaly postnatally is different, namely an HC ≤ -2 SD the mean for gender and age [28], and more often a clinical description by a pediatrician. Because the Fenton growth chart is based on the recommended growth goal for preterm infants, the fetus, followed by the term infant [10], this growth chart seemed most reliable and was used in this study.

Conclusion

We conclude that fetuses identified by ultrasound in the mid-trimester with HC > -3.0 SD and < -1.64 SD (equal to $\leq$2.3th percentile [1]) without suspicion of structural anomalies need follow-up and special medical attention. Distinction between ISHC vs. SHC+ and SHC + D can be helpful for prenatal obstetric and genetic counseling. Offering genetic diagnostic testing should be included in prenatal counseling. Referral to a clinical geneticist for WES counseling can be considered, while further studies on the value of WES need to be performed. Additional monitoring of fetal growth throughout pregnancy is important, as FGR often develops during these pregnancies. In case of an ISHC, with normal follow-up growth rates and after additional prenatal genetic testing with normal results, patients could be referred back to normal obstetric care. Future research should focus on long-term developmental follow-up to investigate the impact of a small HC on neonatal and child development.

Ethical approval

Approval of the study was obtained from the regional Medical Ethical and Institutional Review Board of the Erasmus MC, University Medical Center in Rotterdam (MEC 2020-0412).

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CRediT authorship contribution statement

Sofie C. Husen: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Eline F. Visser:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Malgorzata I. Srebniak:** Resources, Writing – review & editing. **Karin E.M. Diderich:** Resources, Writing – review & editing. **Irene A.L. Groenenberg:** Conceptualization, Writing – review & editing. **Régine P.M. Steegers-Theunissen:** Conceptualization, Methodology, Writing – review & editing. **Attie T.J.I. Go:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The data underlying this article can be shared on reasonable request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2024.01.010.

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